Synthesis Of Some New Phosphate Esters Containing Three 1,3,4-Oxadiazole Units and Studying Thier Biological Activity

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(NJC)

(Received on 15/2/2005) **(Accepted for publication on 4 / 9 /2005)**

Abstract

Condensation of three equivalents of *p*-cresol with phosphorus oxychloride afforded tri (*p*-cresyl) phosphate [1]. Oxidation of the three methyl groups in compound [1] was carried out using potassium permanganate in pyridine yielded tri (4-carboxyphenyl) phosphate [2]. This compound underwent addition–cyclodehydration reactions with 4-methoxybenzoyl hydrazine to produce tri-[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl) phenyl] phosphate [3].

The 5-(4-hydroxyphenyl)-1,3,4-oxadiazole-2-thiol [5] was obtained by the reaction of 4-hydroxybenzoyl hydrazine [4] with carbon disulfide under basic condition. Reaction of compound [5] with appropriate alkyl halide afforded 5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-thio alkyl [6 – 8]. Condensation of three equivalents of appropriate phenolic compounds [6 – 8] with phosphorus oxychloride in the presence of pyridine as proton accepter yielded tri-[4-(5-alkyl thio-1,3,4-oxadiazol-2-yl) phenyl] phosphate [9 – 11].

All the synthesized compounds were characterized by their melting points, and spectral (FT-IR, mass, ^{1}H-NMR and UV) data.

The newly phosphate esters synthesized compounds were subjected to ***in vitro*** testing against two strains of pathogenic microorganism viz., ***Staphylococcus aureus*** and ***Escherichia coli***. The results obtained revealed that compounds [2,9,10 and 11] showed considerable activity against the two types of bacteria, while compounds [1 and 3] showed considerable activity against ***Escherichia coli***.

الخُلاصّة

إنّ تَكاثُف ثَلاثْ مُكافئات مِنْ البارا–كريسول مع أوكسي كلوريد الفسفوريل يُعطي مَنتُوجاً جَيّداً مِن ثُلاثي (بارا–كريسيل) فوسفات [١]. تُعطي أكسَدّة مَجاميع الألكيل الثَلاثّة في المُركّب [١] بأستخدام برمنكنات البوتاسيوم و بوجود البريدين ثُلاثي (٤–كاربوكسي فنيل) فوسفات[٢]. ويَدخل هذا المُركّب تفاعُل الغلَّق الحلَّقي مع ٤–ميثوكسي بنزوايل هيدرازين لينتُج ثُلاثي–[٤–(٥–بارا–ميثوكسي فنيل– ٤,٣,١–اوكسادايازول–٢–يل) فنيل] فوسفات[٣].

تَمّ تَحضير ٥–(٤–هيدروكسي فنيل)–٤,٣,١–اوكسادايازول–٢–ثايول [٥] منْ تَفاعُل ٤–هيدروكسي بنزوايل هيدرازين [٤] مع ثنائي كبريتيد الكاربون تَحتّ ظُروف قاعديّة. ويُعطي تَفاعُل المُركّب [٥] مع هاليدات الكيل مُناسبّة ٥–(٤–هيدروكسي فنيل)– ٤,٣,١–اوكسادايازول–٢–ثايو الكيل [٦ - ٨]. إنّ تَكاثُف ثَلاثْ

مُكافئّات مِن الفينولات المُناسِبّة [٦ - ٨] مع مُكافِئ واحد منْ اوكسي كلوريد الفسفوريل و بوجود البريدين كمُستقبل للبروتّون يُعطي ثُلاثي–[٤–(٥–الكيل ثايو–١,٣,٤–اوكسادايازول–٢–يل) فنيل] فوسفات [٩ - ١١].

لقد تَمّ تَشخيص المُركّبات المُحضّرة مِن خِلال قياس دَرجات إنصهارِها و بأستخدام مُطيافيّة الأشَعّة تحت الحَمراء، كمّا تَمّ الأستعانّة بمطيافيّة الأَشعّة فُوق البنَفسجيةِ–المَرئية و طيف الكتلة و طيف الرنين النووي المغناطيسي في عَمليّة التَشخيص. دُلّتْ النَتائِج المُستحصِلّة على' صِحّة التراكيب المُقترحَة للمُركّبات المُحضّرة.

و أخيراً تَمّ دِراسَة الفعاليِّة البايولوجيّة لِهذه المُركبات المُحضرّة كَأحد التطبيقات ضِد نَوعين مِن البكتريا و هُما البكتريا الموجَبة الصُبغة ***Staphylococcus aureus*** و البكتريا السَالِبة الصُبغة ***Escherichia coli***. و قَد دَلت النتائِج أنَ المُركبات [٢، ٩، ١٠ و ١١] أظهَرت فعالِيّة بايولوجيّة ضِدَ النوعينْ، بَينما المُركبات [١ و ٣] أظهَرت فَعالِيّة ضِدَ ***Escherichia coli*** .

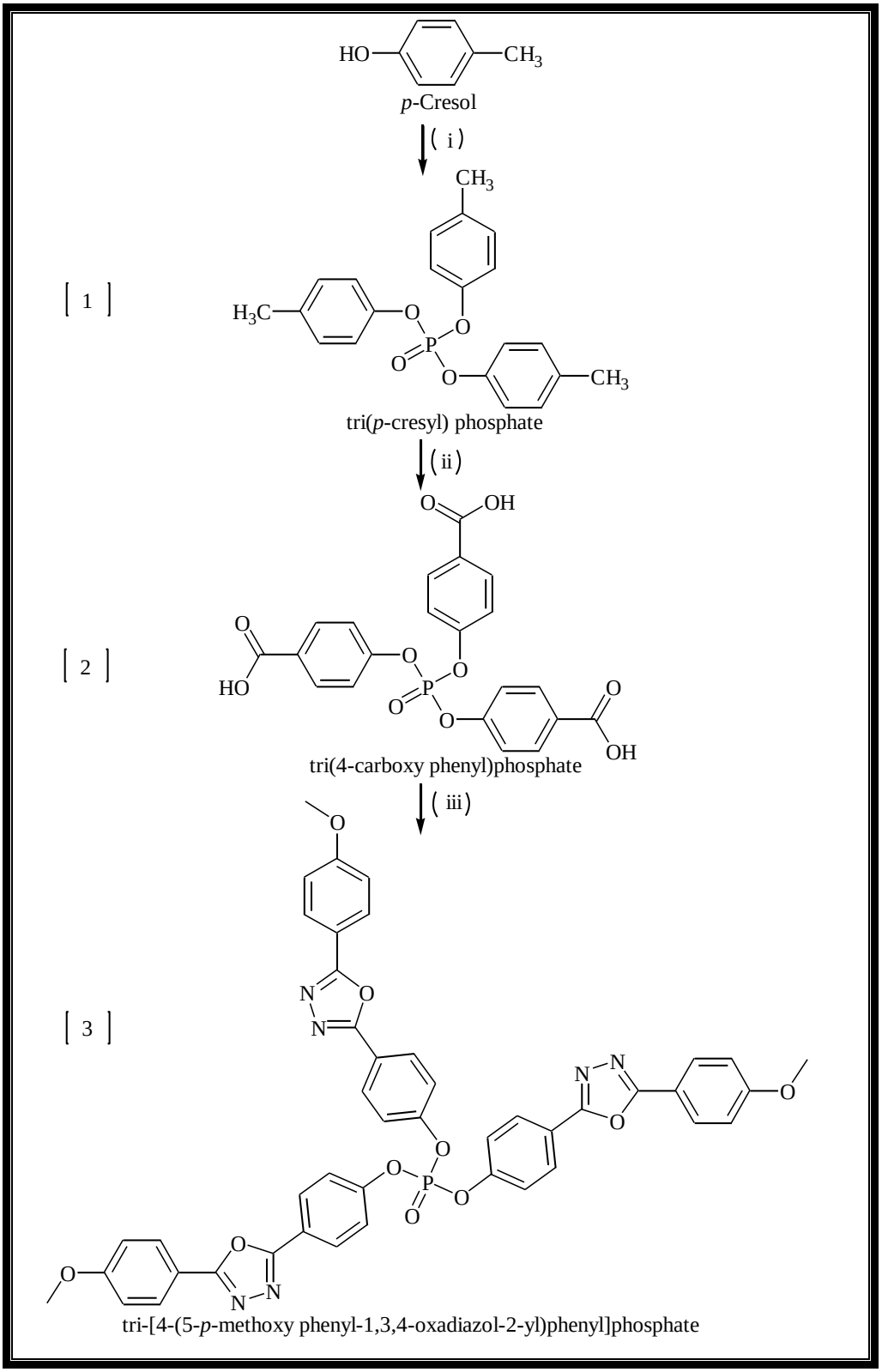
Introduction

The role of organophosphorus compounds in many fields is well known; in the life processes of living organisms, as highly effective agents for controlling agricultural pests; as herbicides and defoliants; as drugs for curing various diseases in medicine and veterinary science; and in industry as plasticizers for polymers, hardeners for film and photo materials, different additives in lubricants and hydrocarbon fuels, admixtures for increasing the incombustibility of compounds, antioxidant and extractants[1].

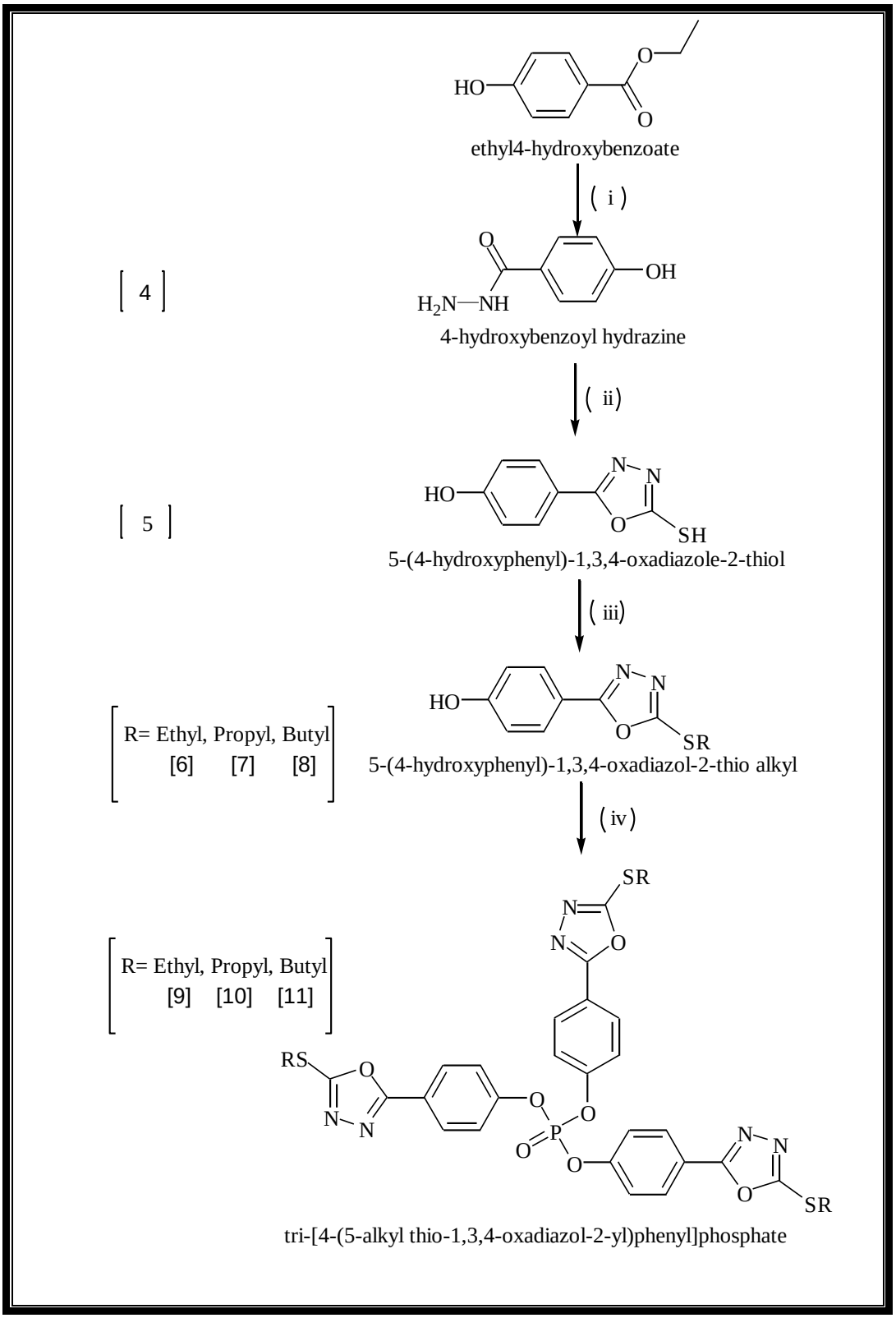
1,3,4-Oxadiazole derivatives constitute an important class of compounds having a wide range of biological activities[2]. In the past years considerable evidence has been accumulated to demonstrate the efficacy of substituted 1,3,4-oxadiazole in antibacterial[3], antifungal[4], antimalarial[5], anticonvulsant[6] and anti-inflammatory[7].

Since organophosphorus compounds containing 1,3,4-oxadiazole are still rare. Therefore, it was decided to synthesize some new phosphate esters containing three 1,3,4-oxadiazole units as showen in Schemes (1 and 2) . with the hope that the incorporation of phosphate ester unit with three biological active. 1,3,4-Oxadiazoles unites may enhance the biological activity of the target molecules.

The synthetic routes for the preparation of the target phosphate esters [3], [9-11] are shown in Schemes (1 and 2), respectively.



Scheme (1) Reagents and conditions:- (i) $POCl_3$, reflux (7) hrs. (ii) Pyridine, H_2O, $KMnO_4$, reflux (5) hrs. (iii) 4-methoxybenzoyl hydrazine, $POCl_3$, reflux (5) hrs.



Scheme (2) Reagents and conditions:- (i) EtOH, CS_2, KOH, reflux (7) hrs. (ii) Appropriate alkyl halide, EtOH, KOH, reflux (4) hrs. (iii) Pyridine, $POCl_3$, chloroform.

Experimental

Instruments

Melting points were measured using **Gallen Kamp** melting point apparatus and were uncorrected. Infrared spectra were recorded on a **Perkin-Elmer 1310 infrared spectrophotometer** and **FT-IR – 8300 fourier transform infrared spectrophotometer SHIMADZU** as potassium bromide disc. UV-Visible Absorbance measurements were recorded on a **Cintra 5 UV-Visible spectrophotometer**. Mass spectra were recorded on **Shimadzu QP1000A** gas chromatography spectrophotometer. The ^{1}H-NMR spectra recorded on **Brucer 60MHz** NMR spectrometer. Deuterated dimethylsulfoxide solution was used as internal solvent.

Synthesis

Preparation of tri (*p*- cresyl) phosphate [1].

This compound was prepared by refluxing *p*-cresol (3 mole, 31.37 ml) at 150 ^{0}C. After 30 minutes phosphorus oxychloride (1 mole, 9.13 ml) was added dropwise with stirring. The mixture was refluxed for (7) hours at (250-300) ^{0}C. The product was suspended in solution of NaOH (2%) and was sterilized for 15 minute. The precipitate which represents the product was filtered and recrytallized from ethanol, yield (88) %, M.P.=(74-76)^{0}C.

Preparation of tri (4-carboxyphenyl) phosphate [2].

Compound [1] (5 g) was dissolved in (75 ml) of pyridine and (100 ml) of H_2O. Potassium permanganate (25 g) was gradually added. The reaction mixture was refluxed for (5) hours and cooled. The solvent was evaporated and the cold reaction mixture was poured on crushed ice and made acidic by adding hydrochloric acid solution. The resulting solid was filtered and dried, yield (37) %, M.P.=(228-230)^{0}C.

Preparation of tri-[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl) phenyl] phosphate [3].

A mixture of compound [2] (0.2 g, 0.00044 mole), 4-methoxybenzoyl hydrazine (0.22 g, 0.00131 mole) and phosphorus oxychloride (4 ml) was refluxed for (5) hours. The cold reaction mixture was poured on crushed ice and made basic by adding sodium bicarbonate solution. The separated product was filtered off and recrystallized from (chloroform – petroleum ether) to give compound [3], (Scheme 1), yield (60) %, M.P.=(241-243)^{0}C.

Preparation of 4-hydroxybenzoyl hydrazine [4].

A mixture of methyl 4-hydroxybenzoate (0.05 mole, 8.3 g) and hydrazine hydrate (0.1 mole, 5 ml) were refluxed for (2) hours, ethanol (15 ml) was added and refluxed for (5) hours. The precipitate which separated on cooling was filtered and washed with cold methanol, yield (77) %, M.P.=(268-270)^{0}C.

Preparation of 5-(4-hydroxyphenyl) -1,3,4-oxadiazol -2-thiol [5].

To a solution of 4-hydroxybenzoyl hydrazine (0.02 mole, 3.04g) in ethanol (100 ml) at 0 ^{0}C, carbon disulfide (0.04 mole) and potassium hydroxide (0.02 mole, 1.12g) were added. The mixture was refluxed for (7) hours. The solvent was evaporated and the residue dissolved in water and acidified with dilute hydrochloric acid. The precipitate was filtered off and crystallized from (ethanol-water), yield (79) %, M.P.=(220-223)^{0}C.

Preparation of 5-(*p*-hydroxyphenyl)-1,3,4-oxadiazol-2-thio alkyl [6-8].

To a stirred solution of compound [5] (0.01 mole) in (25 ml) of ethanol, (0.01 mole, 0.56 g) of KOH was added slowly. The appropriate alkyl halide (0.01 mole) was added dropwise with stirring. The reactants were refluxed for (4) hours. After cooling, the residue was poured into ice-water. The crude product was recrystallized from ethanol to give the desired product, yield (70 – 84) %, M.P.=(148-150)^{0}C for compound [6] , (165-167)^{0}C for compound [7] and (110-112)^{0}C for compound [8].

Preparation of tri-[4-(5-alkyl thio-1,3,4-oxadiazol-2-yl) phenyl] phosphate [9-11].

To a solution of appropriate phenolic compounds (3 mmole) in chloroform (50 ml), dry pyridine (3 mmole) and (0.1 g) NaCl were added. The mixture was stirred for (15) minutes, (1 mmole) of $POCl_3$ in (15 ml) chloroform was added drop wise to the reaction mixture at 0 ^{0}C. Stirring was continued overnight. The reaction mixture was washed with 2% NaOH solution, solvent was evaporated and the product was recrystallized to give the title compounds [9-11], (Scheme 2), yield (65 – 70) %, M.P.=(over 330)^{0}C for compound [9] , (182-184)^{0}C for compound [10] and (over 330)^{0}C for compound [11].

Results and Discussion

The first attempt to build-up the target unknown molecule, tri–[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl)phenyl]phosphate, Scheme (1) was started with tri (*p*-cresyl) phosphate [1] which was prepared in easier fashion by condensation of phosphorus oxychloride with three equivalents of *p*-cresol at elevated temperature. The structure of this compound was identified by its melting point (76 ^{0}C), Lit. [8] (77 ^{0}C) and by infrared spectroscopy.

The FT-IR spectrum of this compound [1], was devoid of the hydroxy band at (3400 – 2500 cm^{-1}) present in the spectrum of *p*-cresol. The presence of a phosphoryl (P=O) group in compound [1] is recognizable by the presence of a medium to strong absorption band at (1303.8 cm^{-1}) also the P-O-C (aromatic) band is observed at (1188.1cm^{-1}).

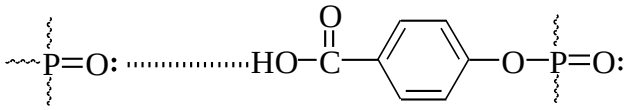
Evidence of the presence of aromatic ring was the presence of (C=C) aromatic stretching band at (1504.4 cm^{-1}) and also a sharp band at (827.4 cm^{-1}) that was assigned to the out-of-plane bending of *p*-disubstituted benzene ring.

The ultra-violet-visible spectrophotometry technique is also used to characterize the synthesized compounds in dimethyl sulfoxide solvent.

The ultra-violet-electronic spectrum of compound [1], Figure (1) showed an absorption band at (262 nm) which could be attributed to the $\pi - \pi^*$ electronic transition. While $n - \pi^*$ and charge transfer (CT) electronic transition appeared at the wave length (328 nm).

Oxidation of the three methyl groups in compound [1] using potassium permanganate in pyridine gave tri (4-carboxyphenyl) phosphate.

The structure of this compound [2] was conformed by its higher melting point (230 ^{0}C) and by its FT-IR spectrum, which display broad, (O-H) stretching absorption in the region (3500 – 2400 cm^{-1}), as well as the carboxylic acid (C=O) absorption at (1697.2 cm^{-1}), the absorption of the phosphoryl (P=O) at (1242.1 cm^{-1}) is significantly lowered and becomes very much broad compared with the absorption of the phosphoryl group of compound [1], this probably due to the presence of the intermolecular hydrogen bonding.



The electronic spectrum of compound [2], Figure (2) displays three prominent bands at (271, 374 and 548 nm). These could be assigned to $\pi - \pi^*$, $n - \pi^*$ and charge transfer transitions, respectively.

As might be anticipated from the change in spectral characteristic, when the spectrum of compound [1] is compared with the spectrum of compound [2], the oxidation of CH_3 group to another chromophoric group–COOH resulted in a shift of the absorptions $n - \pi^*$, $\pi - \pi^*$ and CT in compound [2] to longer wave length.

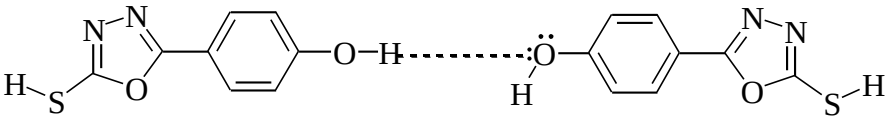
Tri–[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl) phenyl] phosphate was prepared by the condensation of compound [2] with three equivalents of 4-methoxybenzoyl hydrazine in the presence of phosphorus oxychloride. The structure of this oxadiazole compound [3] was assigned on the basis of spectral (UV, FT-IR) data. The FT-IR spectrum of compound [3], Figure (3), was devoid of the amide bands present in the spectrum of the 4-methoxybenzoyl hydrazine at (3300 and 3160 cm^{-1}) as well as the disappearance of the O-H band at (3500-2400 cm^{-1}) of compound [2].

The appearance of a band at (1610.5 cm^{-1}) assignable to (C=N) band of oxadiazole moiety and a band at (1257.5 and 1099.3 cm^{-1}) assigned for (C-O-C) cyclic grouping in oxadiazole are good evidence for the presence of 1,3,4-oxadiazole ring in compound [3]. The presence of a (P=O) group in a target molecule [3] is recognizable by the presence of a medium to strong absorption band at (1301 cm^{-1}). The (P-O-C) (aromatic) band is characterized by two absorption band at (1174.6 and 1026.1) cm^{-1}, respectively.

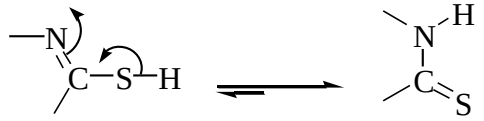
The electronic spectrum of compound [3], Figure (4) showed three bands at (291, 323 and 351 nm) which may be assigned to $\pi - \pi^*$, $n - \pi^*$ and charge transfer transition, respectively. These electronic spectral features are similar to those reported for 2,5-disubstituted 1,3,4-oxadiazoles [9].

The second attempt to build-up the target novel molecules, tri–[4-(5-alkyl thio-1,3,4-oxadiazol-2-yl) phenyl] phosphate, Scheme (2). The convenient starting material was 4-hydroxybenzoyl hydrazine [4], which in turn was prepared from the reaction of 4-hydroxyethyl benzoate and hydrazine hydrate[10].

5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-thiol was prepared through the reaction of compound [4] with carbon disulfide in the presence of potassium hydroxide in 95% ethanol. The structure of this compound, Figure (5) was confirmed on the basis of its melting point (220 – 223 ^{0}C), Lit. [11] (223 ^{0}C) and FT-IR spectroscopy. The FT-IR spectrum of this compound exhibited a sharp band in the region (1610.5 cm^{-1}) which was clearly attributable to υ(C=N). The broad intense band, which is centered at (3172.7 cm^{-1}) is due to υ(O-H), the broading may be attributed to intermolecular hydrogen bonding.

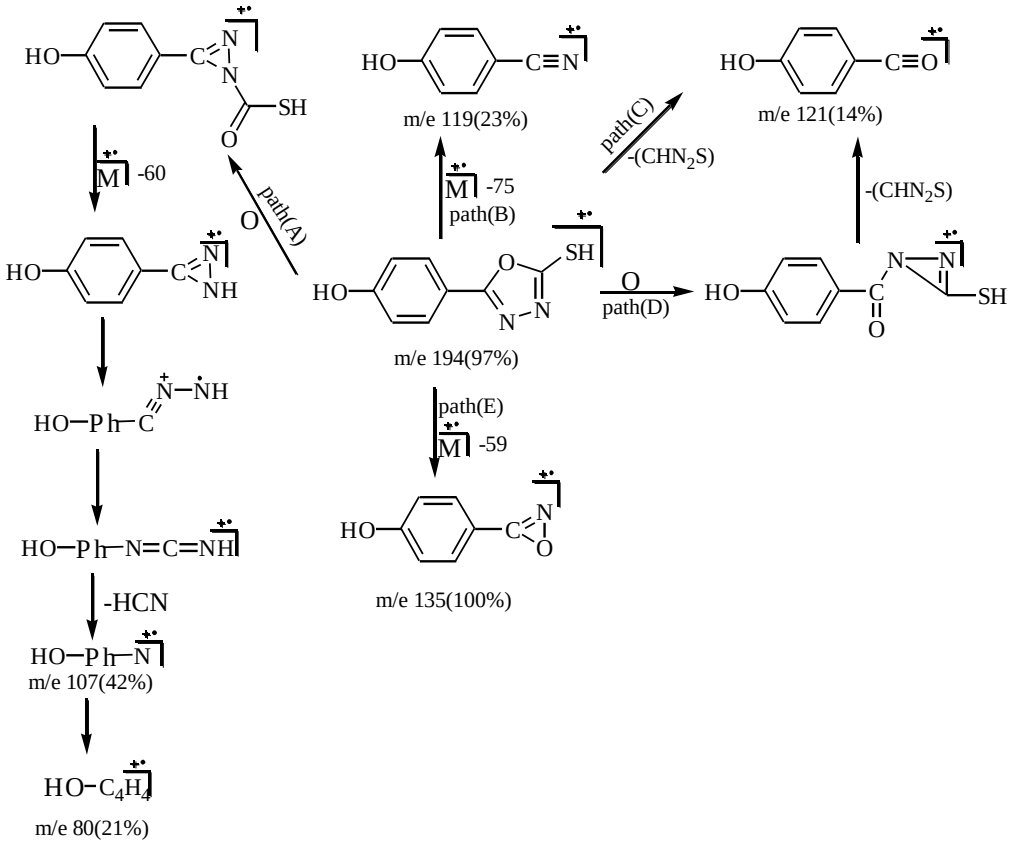


The presence of strong band at (1350.1 cm^{-1}) showed that compound [5] exists predominantly in the thione–form. A very weak band at (2550 cm^{-1}), however, indicated the presence of thiol–form in the tautomeric mixture.



In addition, this compound revealed in absorption band at (835 cm^{-1}) due to para disubstituted benzene nuclei.

The mass spectrum of compound [5], Figure (10) give strong intense molecular ion at 194 which correspond to the molecular weight of the structure assigned to this compound. The spectrum of compound [5] shows interesting ion[12] at m/e 121 $HO-C_6H_4-C\equiv O^{+\bullet}$, Scheme (3) this ion may be formed by direct fragmentation, path (C) or via a diazirine intermediate, path (D). The path (B) and $M^{+\cdot}$-59 path (E) may also be explained in terms of the diazirine intermediate or by direct fragmentation[13]. Scheme (3) represent the fragmentation pattern of compound [5].



Scheme (3) Fragmentation pattern of compound [5].

^{1}H-NMR spectrum of compound [5], Figure (11) showed the following characteristic chemical shifts (DMSO-d^6, δ), sulfhydryl proton at 2.12, N-H proton shows abroad absorption at (3-4). Four aromatic ring protons of (AB) system appear as two doublets leaning towards each other which are typical for *p*-disubstituted rings, the two protons ortho to the hydroxy group absorb at (7.61-7.78) and the two other protons absorb at (6.87-7.00). O-H proton is found at 10.46. The above data agree with the proposed structure .

The 5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-alkylthio [6-8] were prepared through the reaction of potassium salt of 5-(4-hydroxyphenyl)-1,3,4-oxadiazole-2-thiol with appropriate alkyl halide, resulted in the formation of the alkylated thio ethers.

The structures of the synthesized compounds were confirmed by their melting points, (UV and FT-IR) spectral data, the melting points of these compounds [6-8] were in agreement with those reported in the literature [11].

The characteristic absorption bands of the alkylated compounds are shown in Figure (6). The appearance of the (3000 – 2840 cm^{-1}) band, attributable to the υ(C-H), as well as the disapperance of the υ(S-H) band at (1350 cm^{-1}) in compound [5] are utilized to confirm the structure of the alkylated compounds.

Tri–[4-(5-alkyl thio-1,3,4-oxadiazol-2-yl) phenyl] phosphate [9-11], were obtained in (70 – 75 %) yield by stirring a mixture of appropriate alkylated compound, and phosphorus oxychloride in pyridine at room temperature for (24 hrs.).

The authenticities of these products were confirmed by their melting points, FT-IR spectroscopy and UV spectral data.

The disappearance of υ(O-H) band in the spectra of compounds [9-11], Figure (7) and appearance of a new bands at (1308–1292 cm^{-1}) and (1174 – 1166 cm^{-1}) attributable to the (P=O) and υ(P-O-C) (aromatic) respectively, these results that clearly indicated the success of phosphorlation step.

The electronic spectrum of compound [6], Figure (8) displayed two bands at (281 and 328 nm) assigned to $\pi - \pi^*$ and $n - \pi^*$ transition, respectively.Whereas compound [9], Figure (9) showed the corresponding transitions at (291 nm), the other band shifted to the higher wave length at (365 nm) assigned to the $n - \pi^*$ and charge transfer transitions.

The spectral features of these two compounds were found to be similar to those reported for 2,5-disubstituted 1,3,4-oxadiazoles compounds [14].

Biological activity

The antibacterial activity [15] of the synthesized compounds was determined ***in vitro*** using paper disc method (agar plate diffusion method) against two pathogenic microorganism[16] viz., ***staphylococcus aureus*** (Gram +ve) and ***Escherichia coli*** (Gram –ve). In this method, a standard 5mm diameter sterilized filter paper impregnated with the compound (1mg per 1ml DMSO and 1mg per 10ml DMSO for concentration (1) and (2), respectively) was placed on agar plate seeded with the test organism. The plates were incubated for 24 hours at 37 ^{0}C. The zone of inhibition of bacterial growth were measured in mm depending upon the diameter as shown in Table (1), and Figures (12 and 13).

Compounds [2, 9, 10 and 11] showed considerable activity against ***staphylococcus aureus*** (G^+) and ***Escherichia coli*** (G^-), compounds [1 and 3] showed considerable activity against ***Escherichia coli*** (G^-). However, more detail investigation is required to evaluate their activities against other microorganisms.

Table (1): Antibacterial activity of the synthesized compounds.

Compound No.	*Comp. No. in Figures*	*staphylococcus aureus*		*Escherichia coli*	
DMSO solvent	C	*Conc. (1)* –	*Conc. (2)* –	*Conc. (1)* –	*Conc. (2)* –
1	$1_{(1)}$, $1_{(2)}$	–	–	10mm	10mm
2	$2_{(1)}$, $2_{(2)}$	8mm	12mm	12mm	10mm
3	$3_{(1)}$, $3_{(2)}$	–	–	12mm	12mm
9	$4_{(1)}$, $4_{(2)}$	20mm	12mm	14mm	12mm
10	$5_{(1)}$, $5_{(2)}$	14mm	11mm	16mm	10mm
11	$6_{(1)}$, $6_{(2)}$	19mm	14mm	10mm	10mm

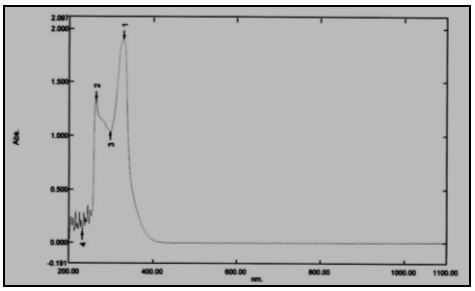


Figure (1): Ultraviolet spectra of tri(*p*-cresyl) phosphate [1].

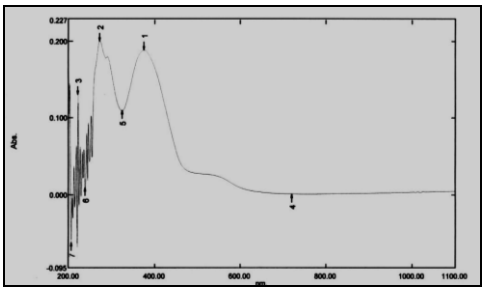


Figure (2): Ultraviolet spectra of tri (4-carboxyphenyl)phosphate [2].

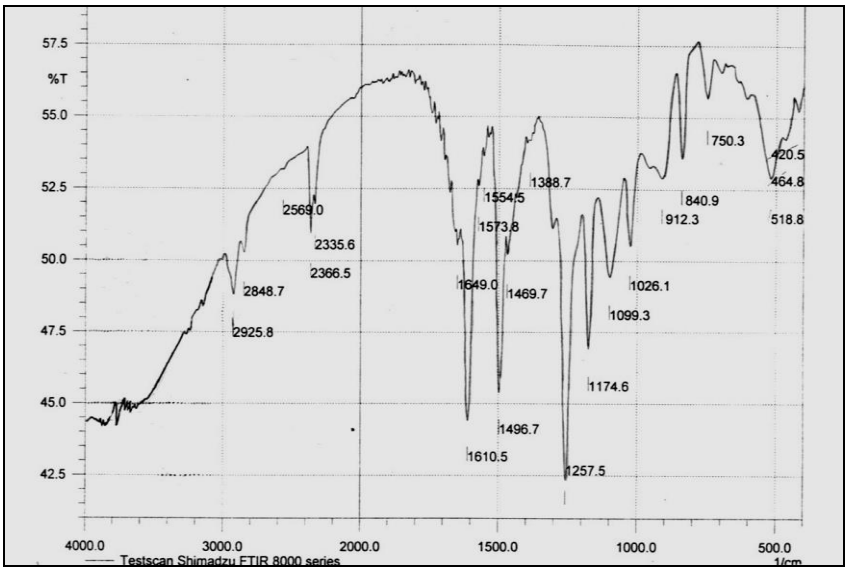


Figure (3): FT-IR spectrum of tri-[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl) phenyl] phosphate [3].

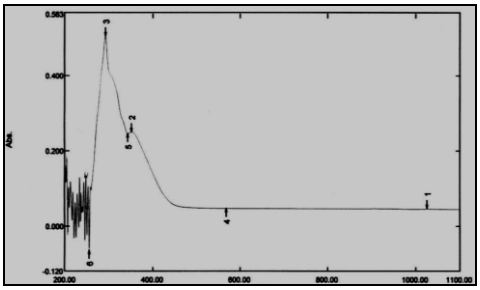


Figure (4): Ultraviolet spectra of tri-[4-(5-*p*-methoxyphenyl-1,3,4-oxadiazol-2-yl) phenyl] phosphate [3].

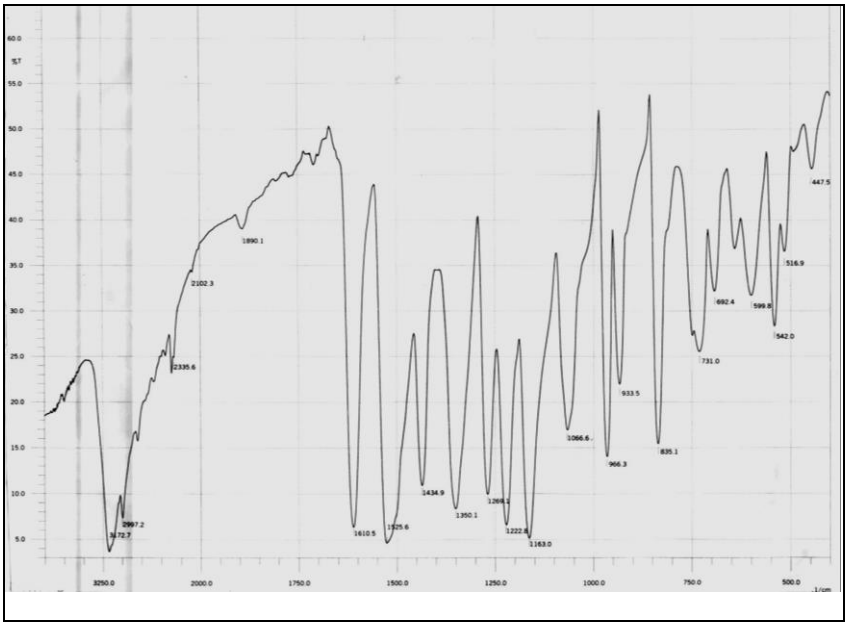


Figure (5): FT-IR spectrum of 4-(hydroxylphenyl)-1,3,4-oxadiazol-2-thiol [5].

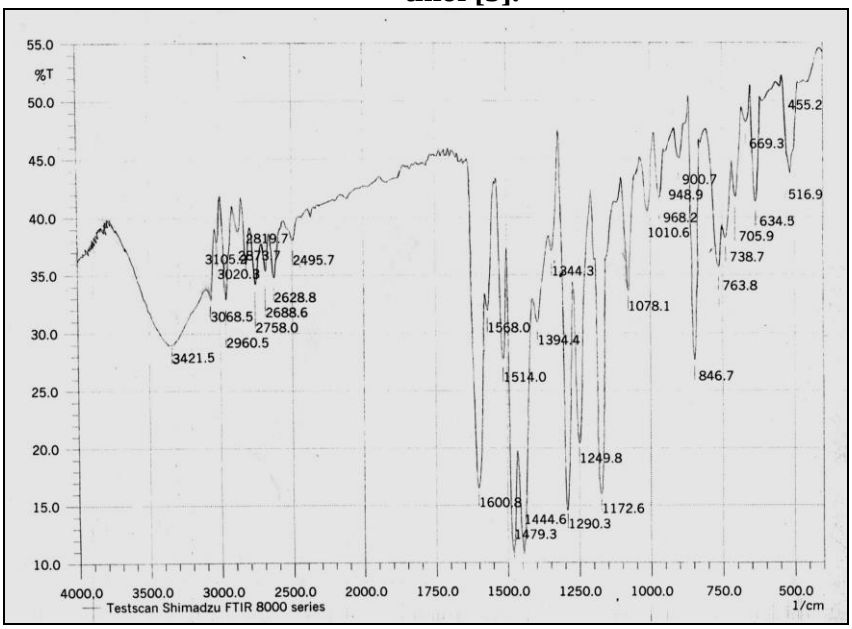


Figure (6): FT-IR spectrum of 5-(*p*-hydroxyphenyl)-1,3,4-oxadiazol-2-thio propyl [7].

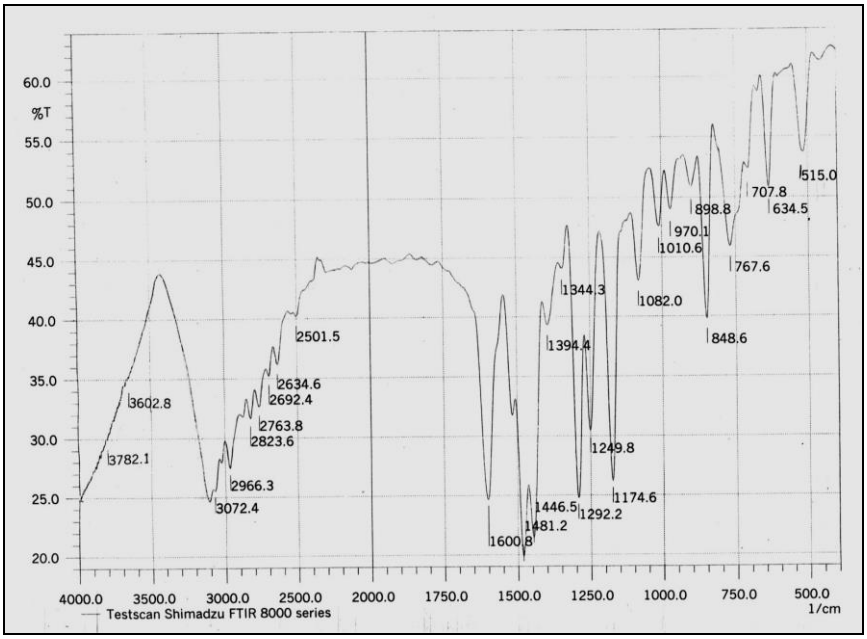
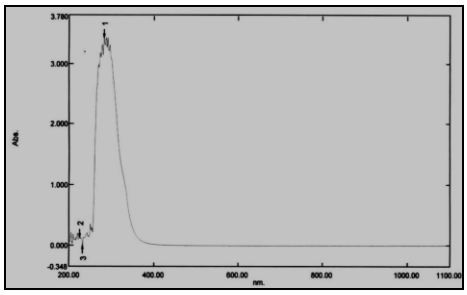


Figure (7): FT-IR spectrum of tri-[4-(5-propyl thio-1,3,4-oxadiazol-2-yl)phenyl] phosphate [10].



Figure(8):Ultraviolet spectra of 5-(*p*-hydroxyphenyl)-1,3,4-oxadiazol-2-thio alkyl [6].

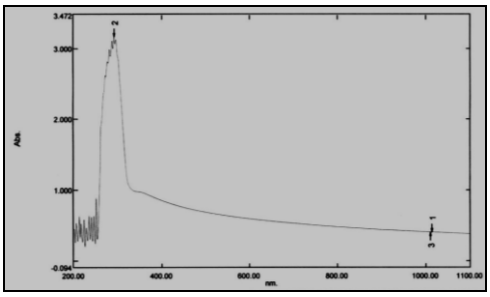


Figure (9): Ultraviolet spectra of tri-[4-(5-ethyl thio-1,3,4-oxadiazol-2-yl) phenyl] phosphate [9].

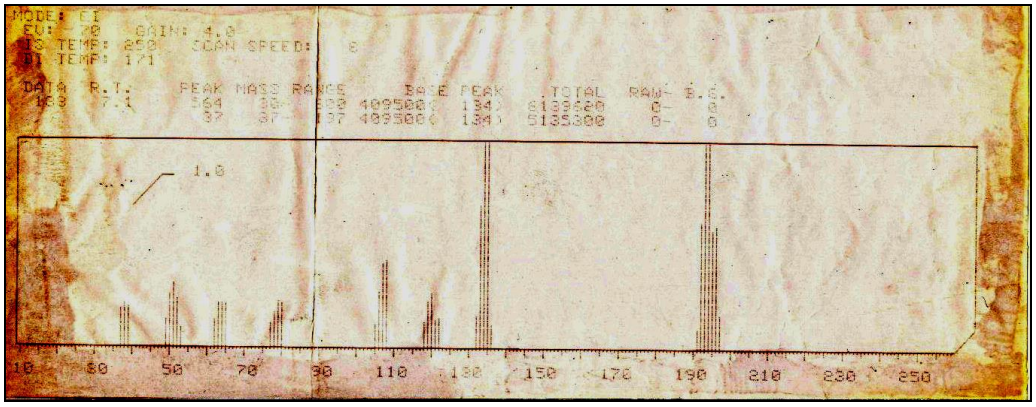


Figure (10): mass spectrum 4-(hydroxylphenyl)-1,3,4-oxadiazol-2-thiol [5].

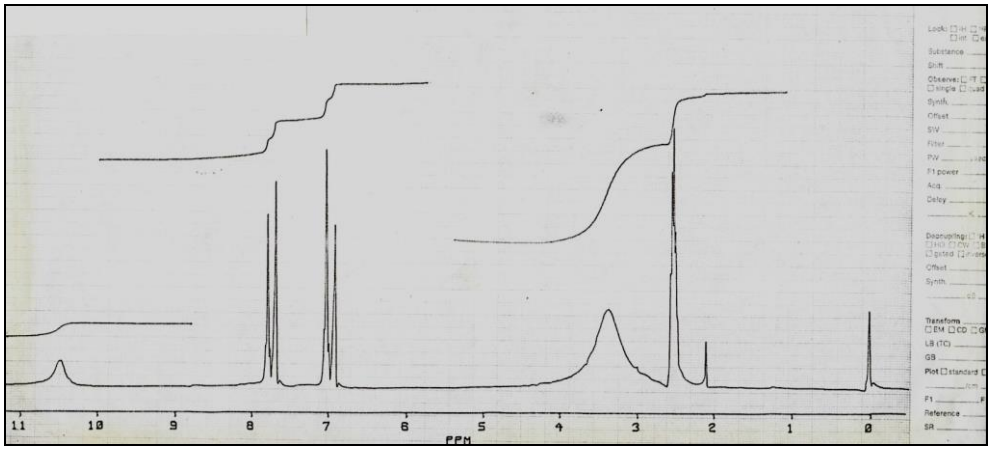


Figure (11): NMR spectrum 4-(hydroxylphenyl)-1,3,4-oxadiazol-2-thiol [5].

Figure (12): Effect of [3], [9], [10] and [11] on Staph.aureus.
$3_{(1)}$ and $3_{(2)}$ = effect of [3], $4_{(1)}$ and $4_{(2)}$ = effect of [9]
$5_{(1)}$ and $5_{(2)}$ = effect of [10], $6_{(1)}$ and $6_{(2)}$ =effect of [11].

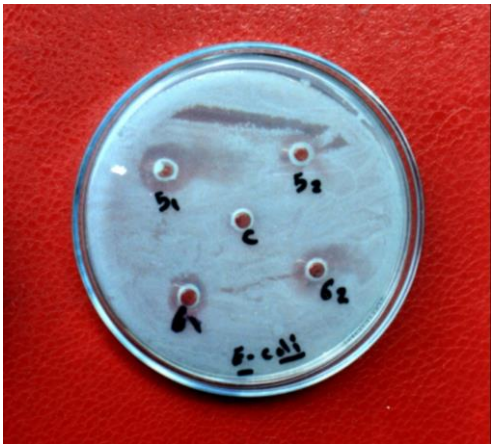


Figure (13): Effect of [10] and [11] on Esch. Coli
$5_{(1)}$ and $5_{(2)}$ = effect of [10], $6_{(1)}$ and $6_{(2)}$ = effect of [11].

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